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Can plasma exchange therapy induce regulatory T lymphocytes in multiple sclerosis patients?

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Summary

Plasma exchange is used increasingly as an individual therapeutic decision for treating of severe, steroid-resistant relapses of multiple sclerosis (MS). However, given that its mechanism of action in this CD4$^+$ T cell-mediated autoimmune disease remains unknown, it is not yet considered as a routine therapy for this prevalent neuroimmune disorder. In this regard, we hypothesized that plasma exchange, by depleting the body of inflammatory mediators that acts as providers of co-stimulatory signals for the adaptive immune system, provides the immune system with an exceptional break for *de-novo* recognition of autoantigens in a tolerogenic manner. This may lead to an increase in the frequency and function of myelin-specific regulatory T cells. For evaluating this we suggest some *in vitro* and *in vivo* studies to analyse the effects of varied dilutions of normal and MS plasmas on the induction of regulatory T cells or on the function of isolated and purified regulatory T cells. Clarifying the effects of therapeutic plasma exchange on regulatory T cells as the major controllers of autoimmune responses may provide us with strong evidence to use this procedure as a disease-modifying treatment in remission phase for reducing the rate and severity of future attacks, in addition to more trustworthy therapy in severe relapses of MS.

Keywords: multiple sclerosis, plasma exchange, regulatory T cell

Introduction

Administration of high doses of intravenous corticosteroids (CS), such as methylprednisolone, is the regular therapy for acute relapses of multiple sclerosis (MS). Although this routine treatment is generally effective for relieving symptoms of an attack in the short term, it does not appear to have a momentous impact on long-term recovery from disease. Additionally, in some patients suffering from severe steroid-resistant relapses, the clinical response to CS therapy may be inadequate. Such patients could obtain clinical benefit from following plasma exchange (PE) therapy. PE is considered increasingly as an individual treatment in patients with severe relapses not responding appropriately to CS. However, because of the lack of proper studies and the unknown mechanism of action, PE is not carried out as an enduring disease-modifying strategy in MS patients [1], while it is an established therapy for the treatment of many other neuroimmune disorders, such as myasthenia gravis, Lambert–Eaton syndrome, Guillain–Barré syndrome and chronic demyelinating polyneuropathy [2,3]. The purpose of the PE procedure is to deplete the blood of various immunological factors, such as antibodies, complement components, chemokines, cytokines and almost all known and unknown inflammatory factors with which their over-production in the patient's body may be associated with the initiation or progression of the disease process [1]. Clearly, this mechanism cannot directly cause all the improving effects of plasma exchange in a cell-mediated autoimmune disease such as MS, in view of the fact that these soluble factors are made by cells and the original producer cells will still be in the body after plasmapheresis is completed. In this regard, some previous studies have shown that plasmapheresis, in addition to depleting the antibodies and other soluble factors from the blood, may affect the frequency and phenotype of different immune cell populations [4–10], and also the function of these cells and production of some cytokines and other soluble factors [11–16]. Regulatory T cells are known as the most important players in maintaining immune system homeostasis and tolerance to self-antigens [17,18], and are also accepted as the main controllers of MS [19–21]. One study has shown that the plasmapheresis treatment of systemic lupus erythematosus (SLE) patients induced a significant increase in the number of peripheral

$CD4^+CD25^{(high)}$forkhead box protein 2 ($FoxP3^+$) regulatory T cells in parallel to the decrease in disease activity [22]. According to these studies, it seems reasonable to suppose that one mechanism by which plasmapheresis exerts its effect on $CD4^+$ T cell-mediated autoimmune diseases such as MS may be through exertion of some effects on the frequency, ratio and function of regulatory T cells.

The hypothesis

By depleting the body of inflammatory factors, plasmapheresis may give the immune system an opportunity to re-adjust itself. This may be possible in part via induction of regulatory T cells through reducing the inflammatory cytokines found in the patients' plasma. According to the established 'two-signal' theory in basic immunology, it has long been accepted that immune activation of T cells is irrefutably dependent upon receiving co-stimulatory signals as the second signal in addition to specific antigen recognition by the T cell receptor complex as the primary stimulatory signal [23]. The B7/CD28 ligand/receptor system is one of the most important co-stimulatory pathways. Any disruption occurring in this signalling pathway results in suppression of the immune responses by induction of functional unresponsiveness or anergy in stimulated T lymphocytes, and in some cases brings about antigen-specific tolerance [24]. Soluble inflammatory factors and cytokines of the innate immune system are the most important regulators of the expression of co-stimulatory molecules, such as B7 family members, on the surface of antigen-presenting cells (APCs) [24–26]. Thus, in the presence of inflammation, antigen recognition by specific T cells is often associated with immune activation, whereas in the absence of inflammatory factors the same antigen recognition can cause the induction of tolerance and unresponsiveness in these antigen-specific T cells and confer upon them the phenotype and function of regulatory T cells. Because plasma exchange washes the body of inflammatory agents, or at least dilutes them in the blood and therefore in the whole body, it may provide naive autoreactive T lymphocytes with the opportunity of recognizing related self-antigens without adequate co-stimulatory signals in a tolerogenic *de-novo* manner. This may cause an increase in the induction of inducible subpopulations of myelin-specific regulatory T cells and also some improvement in the function of naturally occurring regulatory T cells and pre-existing inducible regulatory T cells because of the changes in their cytokine milieu.

Evaluating the hypothesis

For investigating these probable effects, we suggest some *in vitro* and *in vivo* studies, as follows:

1. *In vitro* studies to examine the effects of varied dilutions of plasma or serum on the phenotype and inhibitory functions of regulatory T cells;
2. To examine the effects of MS patients' plasma or serum on the phenotype and regulatory function of these cells in comparison with plasma or serum of healthy individuals; and
3. *In vivo* studies comparing the relative frequency and inhibitory function of these cells before and after plasma exchange therapy course in animal models or in MS patients.

Implications of the hypothesis

If sufficient scientific evidence is provided to confirm positive effects of plasmapheresis on the frequency and function of regulatory T cells, this treatment will have the potential for reducing the rate and severity of future relapses in MS patients, in addition to relieving the symptoms of a present attack. Also, if this hypothesis is proven, continuing efforts can be proposed for specified filtering of the blood and depleting the body of defined inflammatory factors that contrast with the induction or function of these cells, instead of replacing the whole plasma, to perform a more effective and safe treatment for MS and similar autoimmune disorders.

Disclosure

The authors declare that they have no competing interests.

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